



PATENT
Customer No. 22,852
Attorney Docket No. 2405.0190-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:)
Joost VAN NEERVEN) Group Art Unit: 1641
Serial No.: 09/467,901) Examiner: Pensee T. Do
Filed: December 21, 1999) Confirmation No.: 2936
For: A METHOD OF DETECTING) Mail Stop AF
AND/OR QUANTIFYING A)
SPECIFIC IGE ANTIBODY IN A)
LIQUID SAMPLE)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PRE-APPEAL BRIEF REQUEST FOR REVIEW

In response to the Final Office Action mailed April 6, 2005 ("OA"), and the Advisory Action mailed September 8, 2005 ("AA"), Applicant respectfully requests reconsideration of this application in view of the following remarks. A Notice of Appeal is filed concurrently herewith. Claims 1-6 and 8-23 are pending. Two obviousness rejections remain.

The Examiner has applied four references against the pending claims. None, however, contemplate the claimed methods. The Applicant's invention, by virtue of its unique combination of reagents and steps, mimics *in vivo* interactions between IgE, its ligand, and IgE receptors. It does so by recognizing that IgE receptors can have a biological function because of its presence on specific cell types in the body. For

example, by use of an IgE receptor found on a particular cell type the invention can provide insight into the propensity for those cells in the patient to activate and participate in inflammatory responses due to receptor binding. As such, the invention does not simply detect all IgE in a sample. It goes far beyond and targets those IgE available for binding to a free ligand and that can bind to a receptor in the context of other molecules in the sample. The invention's use of IgE receptors provides a level of information beyond that provided by assays that merely detect the presence of IgE antibodies using anti-IgE antibodies. Had this application been properly examined by the Examiner, this would have been evident.

I. Obviousness Rejection in View of Johansen, Johnson, and Frank 2: No Motivation to Combine and No Reasonable Expectation of Success

Claims 1-5, 8-14, 16, and 21-23 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious over Johansen (U.S. Pat. 6,087,188), in view of Johnson (U.S. Pat. 6,034,066) and Frank 2 (U.S. Pat. 6,060,326). AA, p. 2. According to the Examiner, Johansen teaches a method of detecting an antibody using a ligand bound to biotin; an antibody to the antibody to be detected; a chemiluminescent acridinium compound bound to avidin; and a method for quantifying specific antibodies. AA, pp. 2-4. The Examiner then relies on Johnson and Frank 2 for alleged teachings about IgE receptors, asserting that it would have been obvious to combine Johansen's method with IgE receptors allegedly taught by Johnson and Frank 2. AA, pp. 4-5.

None of these three references, however, teach the benefit of mimicking the *in vivo* interactions in an assay to detect or quantify IgE. Nor do these references instruct the artisan to combine a free ligand in a liquid sample with a carrier bound IgE receptor so as to mimic these interactions. On this basis alone, the combination of Johansen,

Johnson, and Frank 2 cannot render these claims obvious.

Regarding the Examiner's alleged basis of rejection, neither Frank 2 nor Johnson motivate one to use the Examiner's combination. The Examiner asserts that the above combination is obvious because CD23 and Fc ϵ RI (two IgE receptors) are specific to IgE antibody, have less cross-reactivity, and are more sensitive over anti-IgE antibodies (citing Frank 2, col. 1, ll. 19-34. AA, p. 5). Unfortunately, the Examiner read a teaching into Frank 2 that isn't there. This cite discusses only the properties of anti-IgE antibodies, not IgE receptors. Thus, the alleged teaching the Examiner relied on for motivation to combine is not present in that reference. Johnson's general teaching of the functions of CD23 in the immune system do not compensate for this deficiency.

Even if the Examiner's interpretation of Frank 2 was accurate, however, the alleged motivation teaches away from the invention. As explained above, the claimed methods mimic *in vivo* interactions between the IgE to be detected or quantified, its ligand, and the IgE receptors. These interactions can include, for example, *in vivo* cross-reactions between IgE receptors and other molecules in a sample. Thus, the alleged motivation based on perception that IgE receptors are specific for IgE and have less cross-reactivity to other molecules is directly contrary to a method that seeks to preserve any cross-reactions that may happen *in vivo*.

Finally, Frank 2 cannot remedy this lack of motivation to combine. The Examiner suggested that Frank 2 uses reagents that are similar to Johansen, and that this perceived similarity would motivate the combination of these references. See Paper No. 082704, pp. 8-9 and Paper No. 032505, p. 8. See Response, 7/6/05, pp. 17-19 for Applicant's response. Applicant notes that the Examiner has also discussed these

citations to Frank 2 in the context of expectation of success. Regarding the Examiner's latest cites to Frank 2 (AA, p. 8), these citations do not address Applicant's point that even if Frank 2 suggests using a particulate in combination with a receptor, it would not necessarily motivate the skilled artisan to use it in the assay of Johansen. Two references that may use similar components, but that does not mean they will work the same way. See Response, 6/16/04, pp. 18-20.

The Examiner misunderstands her obligation to demonstrate a reasonable expectation of success. During this prosecution, the Examiner has relied on Applicant to point out reasons why the combined references would *not* be expected to work. AA, p. 10. But it is the Examiner's initial burden to demonstrate that a reasonable expectation of success exists. Until then, Applicants need not provide such reasons. Applicant respectfully suggests that the Examiner may be confusing the concepts of motivation to combine and expectation of success. See, e.g., AA, p. 9.

II. Obviousness Rejection in View of Johansen, Frank 2, and Arnold: No Motivation to Combine and No Reasonable Expectation of Success

Claims 6 and 17-20 remain rejected under 35 U.S.C. § 103(a) as allegedly obvious in view of Johansen, Frank 2, and in further view of Arnold (U.S. Patent 6,004,745). AA, p. 5. These claims recite methods that use a free ligand, a liquid sample, a carrier bound IgE receptor, and two separation steps. The Examiner uses Johansen and Frank 2 as described above and then adds Arnold to allegedly teach a sandwich assay that uses an immobilized capture antibody and a labeled detection antibody in which two separation steps are used. AA, p. 6.

Arnold does not cure the lack of teaching towards a method of IgE detection or quantification that mimics *in vivo* interactions. Thus, the combination of Johansen,

Frank 2, and Arnold cannot render these claims obvious. Moreover, the Examiner inappropriately used hindsight to provide a connection between Arnold and the other two references. Even if the Examiner's use of Johansen and Frank 2 in the first rejection was correct, which it is not, this analysis did not address the concept of using two separation steps and why there would be a motivation to combine Arnold's two separation steps with Johansen and Frank 2. Applicant explained why no such motivation exists. See Response, 7/6/05, p. 20. The Examiner used her own beliefs about the art to conclude that the skilled artisan "would know" to carry out two separation steps. AA, p. 11.

The Examiner uses her own beliefs about the art to support her contention that a reasonable expectation of success exists. *Id.* Based upon these beliefs, the Examiner concludes that a skilled artisan "would be able to figure out which reagent to use and have a reasonable expectation of success." The Examiner's rationale appears to be based more on opinion rooted in hindsight than on fact.

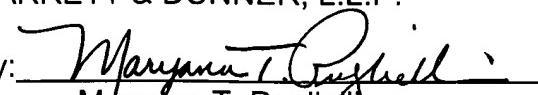
III. Conclusion

In view of the foregoing remarks, Applicants respectfully request reconsideration of this application, the withdrawal of the two remaining obviousness rejections, and the timely allowance of the pending claims. If there is any fee due in connection with the filing of this paper, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

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Date: October 6, 2005

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